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(54) Therapeutic compositions comprising excess enantiomer of amlodipine

(57) The present invention is concerned with pharmaceutical compositions comprising a mixture of amlodipine enantiomers, which compositions have both anti-hypertensive and additional cardiovascular properties derived respectively from their calcium channel-blocking activity and their ability to release vascular nitric oxide (NO).

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Description

[0001] The present invention is concerned with pharmaceutical compositions comprising a mixture of amlodipine enantiomers, which compositions have both anti-hypertensive and additional cardiovascular properties derived respectively from their calcium channel-blocking activity and their ability to release vascular nitric oxide (NO).

[0002] Amlodipine is a well-known calcium channel-blocking agent which is used in the treatment of hypertension and angina. Amlodipine is a dihydropyridine with an assymetric centre at the 4-position; presently, amlodipine is only approved for administration in the form of the racemate, specifically that of the besylate salt.

[0003] The individual enantiomers of amlodipine have been isolated (*J Med Chem* 29 1696 (1986), Arrowsmith *et al*) and identified as R(+) and S(-) (*J Med Chem* 35 3341-3344 (1992), Goldmann *et al*). The calcium channel-blocking activity of the racemate has been found to reside largely, but not exclusively, in the S(-) enantiomer (*J Cardiovasc Pharmacol* 12 (Supp 6) S144, J W Rigby *et al*).

[0004] European Patent No. 0754043 describes the surprising ability of the R(+) enantiomer of amlodipine to inhibit PDGF-induced vascular smooth muscle cell migration using an *in vitro* system which effect may prove to be useful in the treatment of conditions such as atherosclerosis, restenosis after angioplasty and endometriosis.

[0005] It has now been found that the R(+) enantiomer of amlodipine has another unexpected property, specifically the ability to release NO, a potent vasodilator and inhibitor of platelet aggregation and the active species in nitroglycerin (*Kidney International* 49 S2-S5 (1996), Ignarro), from endothelial and vascular smooth muscle cells (hereinafter referred to as "vascular NO").

[0006] When amlodipine is administered as the racemate, the NO-induced cardiovascular effects of the R(+) enantiomer are largely 'masked' by the potent anti-hypertensive effects of the S(-) enantiomer. Furthermore, the amount of racemate which may safely be administered is limited by the hypotensive activity of the S(-) enantiomer which, in excess of about 0.5 mg/kg, can give rise to adverse effects such as a marked and sustained fall in blood pressure and reduced coronary blood flow. The R(+) enantiomer, on the other hand, is expected to provide beneficial cardiovascular effects at concentrations far exceeding those at which the S(-) enantiomer begins to produce unwanted effects. Thus using the racemate of amlodipine places an artificial limit on the amount of R(+) enantiomer which may be administered and deprives the patient of the full cardiovascular benefits of said enantiomer.

[0007] The problem which the present invention seeks to address is to provide amlodipine compositions comprising sufficient S(-) enantiomer to achieve the desired anti-hypertensive and anti-anginal effects while also comprising sufficient R(+) enantiomer to maximise the beneficial NO-induced cardiovascular effects of the latter. That is, to improve blood flow to vital organs such as heart, kidney and brain by vasodilation and inhibition of platelet aggregation without affecting normal haemodynamics.

[0008] Further benefits likely to be associated with such compositions include improved endothelial function, reduced free radical damage, reduced atheroma and plaque lability and a change in the arterio-venous balance. These, in turn, are likely to have significant 'end organ' benefits, for example, reductions in the rate of acute myocardial infarctions and revascularisation associated with coronary heart disease, chronic renal failure, congestive heart failure and angina.

[0009] In work shortly to be published, the ability of the R(+) enantiomer to release vascular NO was studied by

(a) measuring nitrite production in canine coronary microvessels, epicardial coronary artery and aorta; and

(b) measuring cardiac oxygen consumption in canine myocardium *in vitro*

in the presence of increasing concentrations of the enantiomer using the methods described in *Circulation* 97 576 (1998), Zhang and Hintze.

[0010] The R(+) enantiomer gave rise to

(a) a concentration-dependent increase in nitrite production up to about 65 pmol/mg at an enantiomer concentration of 10^{-9}M; and

(b) a concentration-dependent reduction in oxygen consumption (down about 30% at an enantiomer concentration of 10^{-5}M);

both effects were wholly or partly blocked by the NO synthase inhibitor, L-NAME.

[0011] In an identical study, the S(-) enantiomer gave no evidence of nitrite production and, while a reduction in oxygen consumption was observed, it was not blocked by L-NAME.

[0012] As indicated, maximum NO release as measured by nitrite production was observed at a free concentration of R(+) enantiomer of 10^{-9}M or 0.4 ng/ml; this figure corresponds to a plasma protein-bound concentration of about 30ng/ml, that is, some 5x the optimum plasma concentration for the S(-) enantiomer (*Amer J Cardiol* 73 A10-A17 (1994), D N Abernethy *et al*).

[0013] It follows that amlodipine racemate administered for optimum anti-hypertensive effect of the S(-) enantiomer fails to provide sufficient R(+) enantiomer for optimum NO release.

[0014] In a further series of experiments based on the known ability of NO to regulate myocardial glucose up-

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take (*Circ Res* 86 270 (2000), H Tada *et al*), the ability of the R(+) enantiomer to release vascular NO under hypoxic conditions was studied by measuring

(a) the reduction in myocardial glucose uptake (MGU); and

(b) the increase in the time to cessation of beating (TCB)

of hypoxic Langendorff mouse hearts perfused with a 10^{-7}M solution of the enantiomer.

[0015] The R(+) enantiomer produced

(a) a reduction in myocardial glucose uptake of from 0.57 µg/min.mg to 0.27 µg/min.mg, a reduction of over 50%; and

(b) an increase in the time to cessation of beating of from 9 minutes to about 33 minutes.

[0016] The MGU compares favourably with that of a normoxic heart (0.36 µg/min.mg) and indicates that the R(+) enantiomer goes some way towards protecting the hypoxic heart through modulation of myocardial glucose uptake. This was reflected by an increase in TCB of from 9 minutes to about 33 minutes, a three-fold increase in survival time.

[0017] It follows that the dose of amlodipine racemate administered for optimum anti-hypertensive effect of the S(-) enantiomer limits the amount of R(+) enantiomer available for additional protection of the heart from hypoxic damage.

[0018] According to the present invention, therefore, there are provided compositions of amlodipine wherein the amount of S(-) enantiomer present is in the range 1.25mg to 5mg and the ratio of R(+) enantiomer : S(-) enantiomer exceeds the 1:1 ratio found in the racemate. In order to achieve the desired combination of anti-hypertensive and NO-induced cardiovascular effects, the compositions of the invention typically contain a ratio of R(+) enantiomer: S(-) enantiomer in the range 2:1 to 8:1, ideally about 5:1.

[0019] It is also within the scope of the present invention that said compositions may exclusively comprise the R(+) enantiomer when only those cardiovascular effects associated with elevated levels of vascular NO are required, for example, in the treatment of endothelial dysfunction arising from ischaemia and reperfusion of the heart.

[0020] It may also be useful to combine the R(+) enantiomer with a cardiovascular drug of alternative mechanism, for example, an ACE inhibitor, such as ramaprilat or quinapril, to provide an additive or synergistic effect. In this connection, it has been reported that amlodipine racemate and the ACE inhibitor ramaprilat appear to be synergistic in enhancing NO production in canine coronary microvessels (*J Cardiovasc Pharmacol* 35 195-202 (2000), Zhang *et al*) and in regulating myocardial oxygen consumption (*Am J Cardiol* 83 92H-98H (1999), Mital *et al*). Insofar as the amlodipine is concerned, both effects are presumably being manifested through the R (+) enantiomer.

[0021] A similar synergy in NO effect might be expected for the R(+) enantiomer of amlodipine in combination with a PDE5 inhibitor which combination is likely to potentiate the responses to released NO. A particularly preferred PDE5 inhibitor for use in such a combination might be sildenafil.

[0022] The R(+) and S(-) enantiomers used in preparing the compositions of the invention may be prepared by chiral synthesis from a suitable optically pure precursor or obtained from amlodipine racemate by any conventional technique, for example, by chromatographic resolution using a 'chiral' column or by the preparation of diastereoisomers, separation thereof and regeneration of the desired enantiomer.

[0023] Specifically, diastereoisomers may be obtained by reaction of the racemate with a suitable optically active acid or base. The diastereoisomers are then separated, for example, by chromatography or fractional crystallisation, and the desired enantiomer regenerated by treatment with an appropriate base or acid. The other enantiomer may be obtained from the racemate in a similar manner or worked up from the liquors of the first separation.

[0024] The enantiomers used in the preparation of the compositions of the invention are conveniently prepared from the free base of the racemate by means of tartrate diastereoisomers using the methodology described in US Patent No. 5,750,707.

[0025] Each of the resulting enantiomers may be used in the form of its free base or converted to a suitable salt using conventional techniques, for example, by treatment with an appropriate acid. Preferred salts for the purpose of preparing the compositions of the invention include the acetate, besylate, citrate, L-lactate, maleate, malonate, mesylate, phosphate, succinate, D-tartrate and L-tartrate (hemi- or full where relevant).

[0026] The enriched enantiomer mixtures of the present invention may be prepared by (i) combining appropriate amounts of the two enantiomers, (ii) adding an appropriate amount of 'excess' R(+) enantiomer to amlodipine racemate, or (iii) preparing 'mixed' crystals each containing the required ratio of R(+) and S(-) enantiomers. When preparing enriched mixtures in accordance with these methods, it is within the scope of the invention to combine two free bases, a free base and a salt, or two salts. Furthermore, when combining two salts, the salt of one enantiomer may be combined with the enantiomer or racemate of the same or a different salt.

[0027] Compositions according to the invention may be administered alone, but will generally be administered in admixture with a suitable pharmaceutical excipient, diluent, or carrier selected with regard to the intended route of administration and in accordance with stand-

ard pharmaceutical practice.

[0028] For example, the compositions of the invention may be administered orally, buccally, or sublingually in the form of tablets, capsules, ovules, elixirs, solutions, or suspensions, which may contain flavouring or colouring agents, for immediate-, delayed- or controlled-release applications.

[0029] Such tablets may contain excipients, such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants, such as starch (preferably corn, potato, or tapioca starch), sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders, such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

[0030] Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, a cellulose, milk sugar, or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the compositions of the invention may be combined with various sweetening or flavouring agents, colouring matter, or dyes, with emulsifying and/or suspending agents and with diluents, such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

[0031] The compositions of the invention may also be administered parenterally, for example, intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intrasternally, intracranially, intramuscularly, or subcutaneously, or they may be administered by infusion techniques. They are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood. If necessary, the aqueous solutions should be suitably buffered, preferably to a pH of from 3 to 9. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

[0032] For oral and parenteral administration to human patients, the daily dosage level of the composition of the invention will usually be from 2.5 mg to 55 mg in single or divided doses.

[0033] Thus tablets or capsules of the composition of the invention may contain from 2.5 mg to 55 mg of active material and may be administered singly or two or more at a time as appropriate. The physician will determine the actual dosage which will be most suitable for any individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower dosage ranges are merited and such are also within the scope of this invention.

[0034] The compositions of the invention may also be administered intranasally or by inhalation and are conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray, or nebuliser with the use of a suitable propellant, *e.g.* dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane, such as 1,1,1,2-tetrafluoroethane (HFA 134A®) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA®), carbon dioxide, or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray, or nebuliser may contain a solution or suspension of the active compound, *e.g.* using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, *e.g.* sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of a composition of the invention and a suitable powder base, such as lactose or starch.

[0035] Aerosol or dry powder formulations are preferably arranged so that each metered dose or 'puff' contains from 2 mg to 10 mg of the composition for delivery to the patient. The overall daily dose with an aerosol will be in the range of from 2.5 mg to 55 mg which may be administered in a single dose or, more usually, in divided doses throughout the day.

[0036] Alternatively, the compositions of the invention may be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotion, solution, cream, ointment, or dusting powder. The compositions may also be administered transdermally, for example, by the use of a skin patch. They may also be administered by the ocular route, particularly for treatment of the eye.

[0037] For ophthalmic use, the compositions of the invention may be formulated as micronised suspensions in isotonic, pH-adjusted, sterile saline, or, preferably, as solutions in isotonic, pH-adjusted, sterile saline, optionally in combination with a preservative, such as a benzylalkonium chloride. Alternatively, they may be formulated in an ointment, such as petrolatum.

[0038] For topical application to the skin, the composition of the invention may be formulated as a suitable ointment containing the active material suspended or dissolved in, for example, a mixture comprising one or more of the following: mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, they can be formulated as a suitable lotion or cream, suspended or dissolved in, for example, a mixture comprising one or more of the following: mineral oil, sorbitan monostearate, a polyethylene glycol, liquid paraffin, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[0039] Finally, the compositions of the invention may be administered *via* intracavernosal injection.

[0040] The preparation of an enriched enantiomer

mixture in accordance with the present invention and pharmaceutical compositions thereof is illustrated by the following examples:

EXAMPLE 1

PREPARATION OF R(+) AMLODIPINE SALTS FROM RACEMIC AMLODIPINE BESYLATE

(1) PREPARATION OF RACEMIC AMLODIPINE FREE BASE

[0041] To a slight suspension of racemic amlodipine besylate (100.37 g, 0.177 mol) [prepared by the method described in European Patent No. 0244944] in methylene chloride (250 mL, 2.5 mUg) and water (250 mL, 2.5 mUg) was added 11 M sodium hydroxide (24 mL) to achieve pH 13-14. The mixture was stirred for ten minutes during which time it became a solution. The layers were separated and the organic layer washed with water (1x 250 mL) and gravity filtered through a magnesium sulphate (25 g) bed. The magnesium sulphate was washed with methylene chloride (40 mL) and to the combined filtrates was added dimethyl sulphoxide (360 mL). The methylene chloride was removed on a rotary evaporator (45 minutes on a water aspirator followed by 15 minutes under high vacuum).

(2) PREPARATION AND SEPARATION OF R(+) AMLODIPINE TARTRATE DIASTEREOISOMER

[0042] To the dimethyl sulphoxide solution of racemic amlodipine free base obtained in Step (1) was added a solution of L-tartaric acid (6.62 g, 0.044 mol, 0.25 equiv) in dimethyl sulphoxide (360 mL). The solution was stirred at ambient temperature for six hours and the resulting solid collected by suction filtration and washed with acetone (200 mL). (Note: it is important that the dimethyl sulphoxide be completely removed from the solid before the solid is washed with acetone.) The solid was dried *in vacuo* at 50°C overnight to give (R)-amlodipine-hemi-L-tartrate-DMSO-solvate (68.25 g) as a pale yellow, tacky solid. The filtrate was set aside and may be used in the isolation of (S)-amlodipine free base.

(3) PREPARATION OF R(+) AMLODIPINE FREE BASE

[0043] To a solution of the (R)-amlodipine-hemi-L-tartrate-DMSO-solvate (68.25 g) obtained in Step (2) in methylene chloride (345 mL, 5 mL/g) was added a solution of 50% sodium hydroxide (73 mL) in water (72 mL). The solution was stirred at ambient temperature for 40 minutes. The layers were separated and the organic layer extracted with water (1 x 150 mL) and gravity filtered through a magnesium sulphate (25 g) bed. The magnesium sulphate was washed with methylene chloride (40 mL) and the methylene chloride removed on a rotary evaporator using a water aspirator. Heptane was added to the evaporation flask as the volume allowed. Eventually, all of the methylene chloride was removed and 600 mL of heptane was added to the flask. The resulting solid was collected by suction filtration, washed with heptane and dried *in vacuo* at 50°C overnight to give (R)-amlodipine free base (19.4 g, 53.4% yield) as an off-white solid.

Chemical purity by HPLC	99.95%
Chiral purity by HPLC	98.88%

(4) PREPARATION OF R(+) SALTS

(a) SUCCINATE

[0044] To a solution of the (R)-amlodipine free base (1.0 g, 2.45 mmol) obtained in Step (3) in ethanol (15 mL) was added succinic acid (0.29 g, 2.45 mmol) in ethanol (8 mL). The mixture was allowed to stand at ambient t temperature overnight. The resulting solid was collected by suction filtration, rinsed with cold ethanol and dried *in vacuo* at 40°C overnight. An additional 6 hours *in vacuo* at 60°C gave the (R)-amlodipine succinate (1.11 g, 86.0% yield) as a white solid.

(b) MESYLATE

[0045] (R)-Amlodipine free base (1.0 g, 2.45 mmol) obtained in Step (3) was dissolved in isopropyl alcohol (23 mL) after fifteen minutes stirring at ambient temperature. Methanesulphonic acid (0.24 g, 2.45 mmol) in isopropyl alcohol (2 mL) was added and the solution stirred at ambient temperature for 3 hours. After cooling in the refrigerator overnight, a small amount of solid had formed which amount slightly increased after a further night in the freezer. The solid was collected by suction filtration, rinsed with cold isopropyl alcohol and dried *in vacuo* at 40°C overnight. Drying *in vacuo* at 80°C overnight gave the (R)-amlodipine mesylate (1.08 g, 87.4% yield) as a beige solid.

EXAMPLE 2

PREPARATION OF S(-) AMLODIPINE SALTS FROM RACEMIC AMLODIPINE BESYLATE

[0046] S(-) amlodipine succinate and S(-) amlodipine mesylate may be prepared in analogous fashion using, for example, D-tartaric acid rather than L-tartaric acid in Step (2) to prepare and isolate the corresponding diastereoisomer. Alternatively, the L-tartaric diastereoisomer may be worked up from the liquors left after isolation of the R(+) diastereoisomer.

EXAMPLE 3

OPTIONAL PREPARATIONS OF ENRICHED ENANTIOMER MIXTURE

[0047]

(1) To 0.5 mole of R(+) enantiomer free base or a salt thereof prepared by a method in accordance with Example 1 was added 0.1 mole of S(-) enantiomer free base or a salt thereof prepared by a method in accordance with Example 2 and the resulting mixture homogenised.

(2) To 0.2 mole of racemic amlodipine besylate was added 0.4 mole of R(+) enantiomer free base or a salt thereof prepared by a method in accordance with Example 1 and the resulting mixture homogenised.

(3) A solution comprising 0.5 mole of R(+) enantiomer free base or a salt thereof prepared by a method in accordance with Example 1 and 0.1 mole of S(-) enantiomer free base or a salt thereof prepared by a method in accordance with Example 2 was allowed to crystallise and the resulting crystals filtered off.

EXAMPLE 4

SUITABLE FORMULATIONS

[0048]

Tablets	
	mg/tablet
Active ingredient	24.24
Microcrystalline cellulose Ph Eur	50.00
Lactose Ph Eur	121.76
Croscarmellose sodium NF	2.00
Magnesium stearate Ph Eur	2.00

[0049] The active ingredient is sieved and blended with the other components. The resultant mix is compressed into tablets using a rotary tablet press (Manesty Betapress) fitted with 6 mm normal concave punches. The resultant tablets may be film-coated with an appropriate film-coating material.

Capsules	
	mg/capsule
Active ingredient	18.18
Lactose Ph Eur	208.89
Maize starch Ph Eur	69.63

(continued)

Capsules	
	mg/capsule
Colloidal anhydrous silica Ph Eur	0.30
Magnesium stearate Ph Eur	3.00
Fill weight	300.00

[0050] The active ingredient is sieved and blended with the other components. The mix is filled into Size No. 2 hard gelatin capsules using suitable machinery. Other doses may be prepared by altering the fill weight and, if necessary, changing the capsule size to suit.

Claims

1. A pharmaceutical composition comprising an NO-releasing amount of the R(+) enantiomer of amlodipine or of a pharmaceutically acceptable salt thereof, an anti-hypertensive amount of the S(-) enantiomer of amlodipine or of a pharmaceutically acceptable salt thereof and a suitable excipient, diluent, or carrier, **characterised in that** said enantiomers are present in a ratio by weight (based on free base) of R(+) enantiomer: S(-) enantiomer of greater than 1:1.

2. A pharmaceutical composition according to Claim 1 wherein said ratio is less than 10:1.

3. A pharmaceutical composition according to Claim 1 or 2 wherein said ratio is in the range 2:1 to 8:1.

4. A pharmaceutical composition according to any of Claims 1 to 3 wherein said ratio is approximately 5:1.

5. A pharmaceutical composition according to any of Claims 1 to 4 which comprises a mixture of single crystals of the R(+) enantiomer or pharmaceutically acceptable salt thereof and single crystals of the S(-) enantiomer or pharmaceutically acceptable salt thereof in the desired ratio.

6. A pharmaceutical composition according to Claim 5 wherein both enantiomers are in the form of pharmaceutically acceptable salts.

7. A pharmaceutical composition according to Claim 6 wherein the salts of both enantiomers have the same counter ion.

8. A pharmaceutical composition according to any of Claims 1 to 4 which comprises single crystals of the R(+) enantiomer or pharmaceutically acceptable

salt thereof and mixed crystals containing both the R(+) enantiomer and the S(-) enantiomer or pharmaceutically acceptable salts of one or both thereof in the desired ratio.

9. A pharmaceutical composition according to Claims 8 wherein the mixed crystals are racemic.

10. A pharmaceutical composition according to Claims 8 and 9 wherein the R(+) enantiomer is in the form of a pharmaceutically acceptable salt and the enantiomers in the mixed crystals are also in the form of pharmaceutically acceptable salts.

11. A pharmaceutical composition according to any of Claims 8 to 10 wherein the salt of the R(+) enantiomer and the salts of the enantiomers in the mixed crystals all have the same counter ion.

12. A pharmaceutical composition according to any of Claims 1 to 4 which comprises mixed crystals containing both the R(+) enantiomer or pharmaceutically acceptable salt thereof and the S(-) enantiomer or pharmaceutically acceptable salt thereof in the desired ratio.

13. A pharmaceutical composition according to Claim 12 wherein both enantiomers are in the form of pharmaceutically acceptable salts.

14. A pharmaceutical composition according to Claim 13 wherein the salts of both enantiomers have the same counter ion.

15. A pharmaceutical composition according to any of Claims 7, 11 or 14 wherein said counter ion is mesylate or succinate.

16. A pharmaceutical composition according to any of Claims 1 to 15 which is in the form of a tablet or capsule suitable for oral administration.

17. A pharmaceutical composition according to any of Claims 1 to 15 which is in liquid dosage form.

18. A pharmaceutical composition according to any of Claim 1 to 15 which is in the form of a solution suitable for intravenous (IV) administration.

19. A process for the preparation of a composition according to any of Claims 5 to 7 wherein single crystals of the R(+) enantiomer or pharmaceutically acceptable salt thereof are mixed in the desired ratio with single crystals of the S(-) enantiomer or pharmaceutically acceptable salt thereof.

20. A process for the preparation of a composition according to any of Claims 8 to 11 wherein single crystals of the R(+) enantiomer or pharmaceutically acceptable salt thereof are mixed in the desired ratio with crystals containing both the R(+) enantiomer and the S(-) enantiomer or pharmaceutically acceptable salts of one or both thereof.

21. A process for the preparation of a composition according to any of Claims 12 to 14 wherein mixed crystals containing both the R(+) enantiomer and the S(-) enantiomer or pharmaceutically acceptable salts of one or both thereof in the desired ratio are formed by cocrystallisation.

22. The R(+) enantiomer of amlodipine or a pharmaceutically acceptable salt thereof for use in the treatment of a condition for which a vascular NO-releasing agent is indicated.

23. The use of the R(+) enantiomer of amlodipine or of a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a condition for which a vascular NO-releasing agent is indicated.

24. Use according to Claim 23 wherein said medicament is a pharmaceutical composition in accordance with any of Claims 1 to 18.

25. A pharmaceutical composition according to any of Claims 1 to 18 for use in the treatment of a condition for which a vascular NO-releasing agent is indicated.

26. A method of treating a condition for which a vascular NO-releasing agent is indicated which comprises the administration of a pharmaceutical composition in accordance with any of Claims 1 to 18.

27. The use of the R(+) enantiomer of amlodipine or of a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a condition for which both an anti-hypertensive agent and a vascular NO-releasing agent are indicated.

28. Use according to Claim 27 wherein said medicament is a pharmaceutical composition in accordance with any of Claims 1 to 18.

29. A pharmaceutical composition according to any of Claims 1 to 18 for use in a treatment of a condition for which both an anti-hypertensive and a vascular NO-releasing agent are indicated.

30. A method of treating a condition for which both an anti-hypertensive agent and a vascular NO-releasing agent are indicated which comprises the administration of a pharmaceutical composition in accord-

ance with any of Claims 1 to 18.

31. A pharmaceutical composition comprising an NO-releasing amount of the R(+) enantiomer of amlodipine or of a pharmaceutically acceptable salt thereof, an NO-inducing amount of an ACE inhibitor and a suitable excipient, diluent, or carrier.

32. A composition according to Claim 31 wherein said ACE inhibitor is ramaprilat or quinapril.

33. A pharmaceutical composition comprising an NO-releasing amount of the R(+) enantiomer of amlodipine or of a pharmaceutically acceptable salt thereof, an NO-potentiating amount of a PDE5 inhibitor and a suitable excipient, diluent, or carrier.

34. A composition according to Claim 33 wherein said PDE5 inhibitor is sildenafil.

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(57) The present invention is concerned with pharmaceutical compositions comprising a mixture of amlodipine enantiomers, which compositions have both anti-hypertensive and additional cardiovascular properties derived respectively from their calcium channel-blocking activity and their ability to release vascular nitric oxide (NO).

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European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 01 30 6940

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
A	J.LUKSA E.A.: "Pharmacokinetic behaviour of R-(+)- and S-(-)-amlodipine after single enantiomer administration" JOURNAL OF CHROMATOGRAPHY B, vol. 703, no. 1-2, 1997, pages 185-193, XP004100033 * page 185 * * page 192 *	1	A61K31/44 A61P9/12
A	J.LUKSA E.A.: "Semi-preparative chromatographic purification of the enantiomers S-(-)-amlodipine and R-(+)-amlodipine" JOURNAL OF CHROMATOGRAPHY B, vol. 693, no. 2, 1997, pages 367-375, XP004075144 * page 367 * * page 375 *	1	
A	WO 93 10779 A (SEPRACOR) 10 June 1993 (1993-06-10) * claim 1 *	1	TECHNICAL FIELDS SEARCHED (Int.Cl.7) A61K

-/--

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely:

Claims searched incompletely:

Claims not searched:

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
THE HAGUE	20 October 2003	Peeters, J

CATEGORY OF CITED DOCUMENTS

X: particularly relevant if taken alone
Y: particularly relevant if combined with another document of the same category
A: technological background
O: non-written disclosure
P: intermediate document

T: theory or principle underlying the invention
E: earlier patent document, but published on, or after the filing date
D: document cited in the application
L: document cited for other reasons

&: member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

European Patent Office

INCOMPLETE SEARCH
SHEET C

Application Number
EP 01 30 6940

Although claims 26,30 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Claim(s) searched completely:
1-25,27-29,31-34

Claim(s) searched incompletely:
26,30

Reason for the limitation of the search (non-patentable invention(s)):

Article 52 (4) EPC - Method for treatment of the human or animal body by therapy

BNSDOCID: <EP_____1181932A3_L>

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 01 30 6940

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 01 30 6940

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on . The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82